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EXAMINER				
HOLLERAN, ANNE L				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

09/520,130

Applicant(s)

ARATHOON ET AL.

Examiner

ANNE L. HOLLERAN

Art Unit

1643

Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 December 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 54-69 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 54-69 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
- Paper No(s)/Mail Date: _____

- 4) ☐ Interview Summary (PTO-413)
- Paper No(s)/Mail Date: _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

The amendment filed 12/26/2007 is acknowledged. Claims 54-69 are pending and examined on the merits.

Claim Rejections Withdrawn:

Claim Rejections - 35 USC § 112

The rejection of claims 54-69 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendment to the claims.

Claim Rejections - 35 USC § 102

The rejection of claims 64, 65 and 69 under 35 U.S.C. 102(b) as being anticipated by Kostelny (Kostelny, S.A., The Journal of Immunology, 148: 1547-1553, 1992; cited in the IDS) is withdrawn in view of the amendment to the claims.

The rejection of claims 64-66 and 69 under 35 U.S.C. 102(e) as being anticipated by Carter (US 5,731,168; cited in the IDS) is withdrawn in view of the amendment to the claims.

Claim Rejections - 35 USC § 103

The rejection of claims 54, 55, 58-61 and 63 under 35 U.S.C. 103(a) as being unpatentable over de Kruif (de Kruif et al., The Journal of Biological Chemistry, 271(13):

7630-7634, 1996, March; cited in an IDS) as evidenced by Merchant (Merchant, A.M. et al, Nature Biotechnology, 16: 677-681, 1998; cited in IDS), in view of Carter (US Patent 5,731,168; issued Mar. 24, 1998; effective filing date Mar. 1, 1995; cited in an IDS) is withdrawn in view of applicants' statement that Carter cannot preclude patentability of the present invention under 35 USC 103(c)(1), because it would only qualify as prior art under 35 USC 102(e), (f), or (g) and at the time the present invention was made Carter and the instant US Patent Application No. 09/520,130 were owned by Genentech, Inc.

The rejection of claims 54-63 under 35 U.S.C. 103(a) as being unpatentable over de Kruif (de Kruif et al., The Journal of Biological Chemistry, 271(13): 7630-7634, 1996, March) as evidenced by Merchant (supra) in view of Carter (supra) and further in view of Greenwood (Greenwood, J. et al., Ther. Immunol., 1(5): 247-255, 1994) is withdrawn in view of applicants' statement that Carter cannot preclude patentability of the present invention under 35 USC 103(c)(1), because it would only qualify as prior art under 35 USC 102(e), (f), or (g) and at the time the present invention was made Carter and the instant US Patent Application No. 09/520,130 were owned by Genentech, Inc.

The rejection of claims 64-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carter (US 5,731,168; cited in the IDS) in view of Greenwood (supra) is withdrawn in view of applicants' statement that Carter cannot preclude patentability of the present invention under 35 USC 103(c)(1), because it would only qualify as prior art under 35

USC 102(e), (f), or (g) and at the time the present invention was made Carter and the instant US Patent Application No. 09/520,130 were owned by Genentech, Inc.

Claim Rejections Maintained:

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 54-69 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over allowed claims 56-77 of copending Application No. 09/373,403. The rejection is maintained for the reasons of record.

Claims 54-69 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 45-82 of US Patent No. 7,183,076. This rejection was originally a provisional rejection over application no. 10/143,437. The rejection is maintained for the reasons of record.

Applicants have requested that the examiner hold these rejections in abeyance until notice of allowable subject matter.

New Grounds of Rejection:

Claim Objections

Claim 57 is objected to because of the following informalities: “antibody contact domain”. This should be “antibody constant domain”.

Claim 64 is objected to because of the following informalities: “the complementary determining region”. This phrase is objected to for two reasons: 1) the correct phrase is “complementarity determining region”; 2) a light chain has 3 complementarity determining regions (CDRs) and they should be referred to in the plural. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 64-69 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 64 is indefinite because of the phrase “wherein said first polypeptide and said third polypeptide dimerize with said second polypeptide and said fourth polypeptide to form a bispecific antibody. This is confusing because the dimerization should be between the first and the second polypeptide to form the bispecific antibody. The claim already states that the first

and third polypeptides forms one binding domain, and that the second and fourth polypeptides form a second binding domain.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 64-69 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 64-69 are drawn to bispecific antibodies comprising four polypeptides wherein a first and a second polypeptide each comprise a heavy chain constant domain and a heavy chain variable domain and a third and a fourth are each common light chains that are either identical to each other or are identical to each other within the complementarity determining regions (CDRs) and different to each other outside of the CDRs. Bispecific antibodies comprising common light chains where the definition of common light chains is one where the sequences are not identical constitutes new matter.

The basis for this rejection is that the amendment to the specification to recite claims drawn to bispecific antibodies comprising binding domains, where the binding domains are made up of a heavy and light chain, and where the light chain is not the same for all of the binding domains is not supported by the specification. Therefore, the recitation of claim 64 "a third and a fourth of said polypeptides are each common light chains that are either identical to each other

or are identical to each other within the complementary[sic] determining region (CDR) and different to each other outside of the CDR” is not supported by the specification as originally filed. Applicants cite page 23, lines 5-9 as providing support for the amendment to claim 64. However, this passage refers to a process for selecting a light chain to be a common light chain, where the common light chain is compared to light chains of library clones.

The specification teaches methods of making bispecific antibodies, where the each of the binding domains comprises a “common light chain”. The specification defines “common light chain” or “common amino acid sequence of the light chain” on page 21, and as an amino acid sequence of *the* light chain in the bispecific antibody. There does not appear to be any contemplation of bispecific antibodies comprising more than one light chain (i.e., there appears to be only the contemplation that the same light chain is used for all of the binding domains present in the bispecific antibody). Even a difference of 1 amino acid between the two light chains results in a bispecific antibody having two different light chains, and there is no support in the specification that demonstrates that applicant conceived of a method of making bispecific antibodies having two different light chains. Other instances in the specification that indicate that applicant conceived of methods of making bispecific antibodies where all of the binding domains comprise a light chain having the same sequence is found at page 13, lines 14-21; page 22, line 15 – page 23, line 12; page 27, lines 2-5; page 56, lines 10-26; page 95, lines 25-28; and page 104, line 22 – page 105, line 26.

Claim 62 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described

in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 62 introduces new matter into the specification as originally filed. Claim 62 is drawn to a bispecific antibody of claim 61, wherein the multimerization domain of the first polypeptide has a protuberance and the multimerization domain of the at least one additional polypeptide has a cavity, where claim 62 adds the limitation that the multimerization further comprises a non-naturally occurring disulfide bond. Thus, claim 62 is drawn to a bispecific antibody having a multimerization domain with a protuberance and cavity interaction in addition to a disulfide bond. The amendment which originally introduced a claim of this nature was filed October 1, 2003. The passages pointed to by applicant in the remarks accompanying the amendment do not provide support for a bispecific antibody encompassed by claim 62. Furthermore, an examination of the specification does not reveal any support for subject matter of claim 62. Therefore, it does not appear that the inventors were in possession of the invention of claim 62 at the time the application was filed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 54 and 56 are rejected under 35 U.S.C. 102(b) as being anticipated by de Kruif-A (de Kruif, J. et al. *Journal of Biological Chemistry*, 271(13): 7630-7634, 1996;

cited in IDS) as evidenced by de Kruif-B (de Kruif, J. et al, J. Mol. Biol., 248: 97-105, 1995; cited in IDS).

Claims 54 and 56 are drawn to bispecific antibodies that are scFv dimers where one binding domain binds one antigen and the other binding domain binds a second, different antigen, and where the light chain variable domains of the two binding domains have the same sequence. Additionally, the first and second polypeptides of the scFv dimers dimerize by interaction of the first and second multimerization domain, where the multimerization domains each comprise at least a part of a C_H3 domain of an antibody constant region. The phrase "at least a part of a C_H3 domain is broad and encompasses a "part" that is as small as one amino acid. Therefore, this phrase fails to impart any structural definition to the multimerization domains of the claimed bispecific antibodies.

de Kruif-A teaches methods for making bispecific antibodies from semi-synthetic antibody phage display libraries, such as the libraries of Hoogenboom and Winter (1992), Nissim(1994) or of de Kruif (1995) (see page 7632, 2nd column). de Kruif-B provides evidence that libraries such as that of Hoogenboom and Winter(1992) or Nissim(1994) are libraries with collections of V_H genes combined with one light chain (see page 98, column 1, first full paragraph). The bispecific scFv dimers of de Kruif-A all comprise multimerization domains that comprise Fos or Jun leucine zipper and a truncated, flexible murine IgG3 hinge region (see page 7630, first paragraph) as well as cysteine residues added via Gly-Gly spacers, which would allow for the formation of a non-naturally occurring disulfide bond between the first and second polypeptides.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 54, 55, 58-61, and 63 are rejected under 35 U.S.C. 103(a) as being obvious over Carter-B (WO 96/27011; published 6 Sep., 1996; cited in IDS) in view of de Kruif-A (de Kruif, J. et al. The Journal of Biological Chemistry, 271 (13): 7630-7634, 1996; cited in

IDS) and further in view of de Kruif-B (de Kruif, J. et al, J. Mol. Biol., 248: 97-105, 1995; cited in IDS).

The claims read on scFv dimers, where one of the binding domains binds one antigen and the other binding domain binds a second antigen (i.e. bispecific), and where the light chain variable domains of each of the binding domains are identical in sequence.

Carter-B teaches methods of making bispecific antibodies comprising culturing a host cell comprising a nucleic acid encoding a first polypeptide and nucleic acid encoding at least one additional polypeptide, wherein the first polypeptide and the at least one additional polypeptide comprise multimerization domains that contain a heavy chain constant domain forming an interface positioned to interact with an interface of the multimerization domain of the at least one additional polypeptide (page 6, lines 14-44; page 7, lines 10-36). These polypeptides also form binding domains that comprise scFv antibody fragments (page 10, lines 16-25 and lines 37-46; page 11, lines 17-24; and page 19, lines 2-7; page 21, lines 3-17), with one binding domain having one specificity and the other binding domain having a second, different specificity (page 1, lines 11-12; page 4, lines 8-21). The interaction between the multimerization domains comprise a protuberance-into-cavity interaction, which is generated by altering the first polypeptide by substituting an amino acid of the first polypeptide with an amino acid that has a larger side chain volume than the substituted amino acid and the cavity is generated by altering the at least one additional polypeptide by substituting an amino acid of the at least one additional polypeptide with an amino acid that has a smaller side chain volume than the substituted amino acid (page 13, line 39 – page 17, line 20). Carter-B teaches methods for making bispecific

antibodies comprising heavy chain constant domains that are either C_H3 domains or IgG heavy chain constant domains (page 10, lines 22-27 and page 10, line 42 - page 11, line 2).

Carter-B fails to specifically teach that the light chain variable domain for one binding domain formed by the first polypeptide will have the same amino acid sequence as the light chain variable domain for other binding domain formed by the at least one other polypeptide.

However, de Kruif-A teaches methods for making bispecific antibodies from semi-synthetic antibody phage display libraries, such as the libraries of Hoogenboom and Winter (1992), Nissim(1994) or of de Kruif (1995) (see page 7632, 2nd column). de Kruif-B teaches that libraries such as that of Hoogenboom and Winter(1992) or Nissim(1994) are libraries with collections of V_H genes combined with one light chain (see page 98, column 1, first full paragraph).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Carter-B with those of de Kruif-A and de Kruif-B to make the claimed inventions because Carter-B teaches that bispecific antibodies may be made using methods of forming interfaces to promote heterodimerization of two different polypeptides, and because Carter-B teaches that nucleic acids encoding such polypeptides may be derived from known phage libraries. Because de Kruif-A and de Kruif-B show that antibody phage libraries containing multiple heavy chains paired with the same light chain were known in the art and useful for isolating scFv fragments that bound to different antigens, it is clear that the prior art provided antibody phage libraries that encode binding domains that are the same as those of the claimed bispecific antibodies where the sequence of the light chain is the same for each binding domain. While there is no explicit suggestion in Carter-

B to choose one of the libraries provided by de Kruif-A and de Kruif-B, it would have been obvious to try to use the methods of Carter-B, which suggested the use of phage libraries as a source of nucleic acid sequences to encode the binding domains of the first and second polypeptides, with the phage libraries taught by de Kruif-A and de Kruif-B, especially since de Kruif-A suggests that bispecific antibodies may be made from such antibody phage libraries.

Claims 54, 56, 57-60 and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hu (Hu, S.-Z., et al., Cancer Research, 56: 3053-3061, 1996; cited in the IDS) in view of de Kruif-A (supra) and further in view of de Kruif-B (supra).

The claims encompass bispecific antibodies comprising multimerization domains that are made up of a domain from a constant region of an antibody and also a non-naturally occurring disulfide bond, where the antigen binding domains are made of scFv fragments, where one scFv binds one antigen and the other scFv binds a second antigen.

Hu teaches that scFv dimers may be formed by ligating a nucleic acid sequence encoding an scFv domain to a nucleic acid sequence encoding a C_H3 domain with a nucleic acid sequence in between the scFv domain and the C_H3 domain, where the linker sequence encoded a hinge and Gly-Ser sequence, which included two potential disulfide bridges.

Hu fails to teach that the two scFv bind to different antigens (bispecificity). Although the light chains of Hu's scFv domains are the same for each scFv domain this is because the two scFv domains bind to the same antigen.

However, de Kruif-A teaches methods for making bispecific antibodies from semi-synthetic antibody phage display libraries encoding scFv domains, such as the libraries of

Hoogenboom and Winter (1992), Nissim(1994) or of de Kruif (1995) (see page 7632, 2nd column). de Kruif-B teaches that libraries such as that of Hoogenboom and Winter(1992) or Nissim(1994) are libraries with collections of V_H genes combined with one light chain (see page 98, column 1, first full paragraph).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Hu with those of de Kruif-A and de Kruif-B to make the claimed inventions because Hu teaches that scFv dimers may be made using methods of forming interfaces to promote heterodimerization of two different polypeptides. Because de Kruif-A and de Kruif-B show that antibody phage libraries containing multiple heavy chains paired with the same light chain were known in the art and useful for isolating scFv fragments that bound to different antigens and that scFv libraries are useful for finding scFv domains for a bispecific antibody, it is clear that the prior art provided antibody phage libraries that encode binding domains that are the same as those of the recited bispecific antibodies where the sequence of the light chain is the same for each binding domain. While there is no explicit suggestion in Hu to make bispecific scFv dimers or to choose one of the libraries provided by de Kruif-A and de Kruif-B, it would have been obvious to try to combine the methods of Hu, which teaches a method for making an scFv dimer, with the methods of using phage libraries as taught by de Kruif-A and de Kruif-B, to make bispecific scFv dimers as suggested by de Kruif-A.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne Holleran, whose telephone number is (571) 272-0833. The examiner can normally be reached on Monday through Friday from 9:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached on (571) 272-0832. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Official Fax number for Group 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Anne L. Holleran
Patent Examiner
April 8, 2008

/Alana M. Harris, Ph.D./
Primary Examiner, Art Unit 1643